REMARKS

The Official Action mailed September 30, 2002 has been received and carefully reviewed. Claims 13 and 20 are herein amended; while new claims 24-27 have been added, and thus, claims 1-27 of the application are presently pending.

In light of the amendments presented above, as well as the reasons set forth below, reconsideration and withdrawal of the currently pending rejections is requested.

With regard to the Examiner's rejection of claims 20 and 22, under 35 U.S.C. § 112 (first paragraph), on the basis that the specification does not support the features of claims 20 and 22 in the recitation of the phrase "...Formula III produced contains less than 1.0% of 5-chloro-2-alkyl-4-isothiazoline-3-one," the Applicants would specifically point to Working Example 3, at Table 1, in which R of Formula III is methyl and the reaction solvent which exhibits little or no solubility for hydrogen chloride is chloroform. In that Working Example 3, the Applicants specifically teach (see Table 2) that an embodiment within the scope of the claimed invention can yield <1.0% of 5-chloro-2-alkyl-4-isothiazoline-3-one. Note also that the Working Example 2 provides support for the more narrow limitation of "less than 0.5% of 5-chloro-2-alkyl-4-isothiazoline-3-one" of claim 21; while examples 1, 4-7 disclose that the 5-chloro-2-alkyl-4-isothiazoline-3-one can be present at less than 0.1% under certain reaction conditions. In view of such teachings, it is asserted that the Examiner's rejection of claims 20 and 22, under § 112 (first paragraph), has been set forth in error and should be withdrawn.

With regard to the Examiner's rejections of claims 1-23, under 35 U.S.C. 103(a), as being unpatentable over GB 2,308,364 to Kim et al. or U.S. Patent No. 3,849,430 to Lewis et al.., each taken alone or in combination with each other, the Applicants respectfully traverse each of these rejections. Specifically, the Examiner states that Kim et al. in Scheme 5, pages 12-13, teaches the use of Cl_2 or sulfurylchloride as the chlorinating agent in combination with a mixed solvent system (some of which include those exemplified in the instant claims) for reaction with:

n-methyl-3-mercaptopropionamide (A-1), or

N,N dimethyl 3,3'-dithiodipropionamide (A-2),

to yield both 2-methyl-4-isothiazoline-3-one (I) AND 5-chloro-2-methyl-4-isothiazolin-3-one (II) would suggest the claimed invention to one of ordinary skill in the prior art.

However, to make such an assertion is to ignore the very teachings of the Applicants, at pages 3 and 4, and the Working Examples 1-7 of the specification, that the selection of a solvent of a type as claimed when used with chlorine as the chlorinating agent provides a very high selectivity for 2-methyl-4-isothiazoline-3-one over the mutagenic 5-chloro-2-methyl-4-isothiazolin-3-one. The Examiner attempts to show a suggestion or motivation for selecting the claimed use of chlorine along with the claimed solvent by pointing to page 11, lines 13-24, of Kim et al. where it is taught that 2-methyl-4-isothiazoline-3-one can be produced in preference to 5-chloro-2-methyl-4-isothiazolin-3-one by carrying out the process at temperatures of less than 5 °C. However, Kim et al. also teach, at page 11, line 13, that such a composition results in a "biologically ineffective mixture" of 2-methyl-4-isothiazoline-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one. Therefore, one of ordinary skill in the prior art is taught by Kim et al. that when carrying out the process in the range of 5 to 20 °C the desired "biologically active" composition containing both 2-methyl-4-isothiazoline-3-one AND 5-chloro-2-methyl-4-isothiazolin-3-one will be formed. There is no suggestion or motivation in Kim et al. to guide one of ordinary skill in the art to select the claimed use of the particularly claimed chlorinating agent, i.e., chlorine, and a solvent in which hydrogen chloride is insoluble or has low solubility, e.g., dichloroethane, dichloromethane. Every one of the examples 1-23 and comparative examples 1-2 of Kim et al. (Table 1) teaches that the process of Kim et al. will form the mutagenic 5-chloro-2-methyl-4-isothiazolin-3-one in preference to the non-mutagenic 2-methyl-4-isothiazoline-3-one. In fact, one of ordinary skill in the art is taught by Kim et al. to perform the methodology, such as through temperature selection, in order to avoid a preference of 2-methyl-4-isothiazoline-3-one relative to 5-chloro-2-methyl-4-isothiazolin-3-one since to do so would give a "biologically ineffective mixture." Additionally, even the Comparative example 1 of Kim et al. which uses chlorine as the chlorinating agent, along with ethyl acetate as the reaction solvent, teaches the formation of the mutagenic 5-chloro-2-methyl-4-isothiazolin-3-one in preference to the non-mutagenic 2-methyl-4-isothiazoline-3-one.

The Examiner asserts that the Applicants have not shown a comparison with the closest prior art (Comparative Example 1 of Kim et al.) in order to establish a showing of unexpected

results, but in fact the Applicants have made such a showing. Notwithstanding the Applicants' assertion that the Examiner has not established a *prima facie* case of obviousness which may necessitate such a showing, Tables 1 and 2 of Kim et al., at Comparative Example 1, teach that a 3:1 mole ratio of chlorine gas to N-methyl-3-mercaptopropionamide in an ethyl acetate solvent reacted at 35 °C yields a mixture containing the mutagenic 5-chloro-2-methyl-4-isothiazolin-3-one (41 wt%) and the non-mutagenic 2-methyl-4-isothiazoline-3-one (24 wt %); while the Applicants' Comparative Example 1 reacts a 3:1 mole ratio of chlorine gas and N,N'-dimethyl-3,3,-dithiopropionamide in an ethyl acetate solvent reacted at 39 °C to yield a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one (53 mole%) and the non-mutagenic 2-methyl-4-isothiazoline-3-one (47 mole%). In comparison, the Applicants have provided a Working Example 1, which reacts a 3:1 mole ratio of chlorine gas and N,N'-dimethyl-3,3,-dithiopropionamide in a dichloromethane solvent of the claimed invention which is reacted at 39 °C to give a yield of mutagenic 5-chloro-2-methyl-4-isothiazolin-3-one (<0.1 mole%) which is greatly diminished relative to the non-mutagenic 2-methyl-4-isothiazoline-3-one (>99.9 mole%) biologically active compound.

Turning to the Lewis et al. reference, the Examiner asserts the patentees teach forming the 3-isothiazolones presently claimed by oxidation cyclization of either a disulfideamide of Formula III or a mercapto amide of Formula IV (which are the same as the claimed Formulae II and I, respectively) with a halogenating agent selected from the group of chlorine, bromine, sulfuryl chloride, sulfuryl bromide, N-chlorosuccinimide, N-bromosuccinimide, with chlorine and sulfuryl chloride being preferred. The process of Lewis et al. is further carried out in an inert, non-aqueous solvent such as benzene, toluene, xylene, ethyl acetate, ethylene dichloride, 1-nitropropane. The Examiner asserts that the selection by Lewis et al. of the components above in the mole ratio (at column 2, lines 46-64) of halogenating agent to either Formulae III or IV in the starting reaction renders obvious the claimed process of forming 3-isothiazolones of the present invention.

The Applicants respectfully assert that such teachings do not render obvious the claimed method of forming the 3-isothiazolones of Formula III by employing either Formulae I or II (of claims 1, 20 and 24) in conjunction with a chlorine (Cl_2) halogenating agent and a solvent which has little or no solubility for hydrogen chloride in a ratio of halogenating agent to either of

Formulae I or II of 2:1 or 3:1, respectively. Initially, it must be noted that the referenced section (column 2, lines 46-64) of the Lewis et al. only states that cyclization occurs at a mole ratio of 3:1 (halogenating agent to Formula III of Lewis et al.). Such a statement does not infer that halogenated compounds of Formula I of Lewis et al. are not also formed. To the contrary, Example 1 of Lewis et al. clearly points out that when a 3:1 ratio of halogenating agent and Formula III are used that the 3-isothiazolone AND the 5-chloro-3-isothiazolone are formed.

Additionally, Lewis et al. clearly state (column 2, lines 60-62) that when the starting material is of Formula IV, the 3:1 ratio of halogenating agent to Formula IV will result in mono-halogenation of the 3-isothiazolone. This teaching is reflected in the Example 13 of Lewis et al. which shows that, even when using chlorine as the halogenating agent in the claimed 3:1 ratio to the mercaptopropionamide, the use of "ethyl acetate" as the reaction solvent yields a higher proportion of the mono-chlorinated 5-chloro-3-isothiazolone than the 3-isothiazolone. Finally, the Examiner asserts that Example 8 of Lewis et al. would suggest the claimed invention. However, a review of Example 8 indicates that such is not the case since that example does not even use the same starting materials (Formulae I or II) or yield the same end products (Formula III). That is, Example 8 of Lewis et al. begins with an "n-decyl" dipropionamide whereas the claimed invention clearly sets forth for Formula I and II starting material that R is C1 to C8 alkyl or aralkyl groups. Further, Example 8 utilizes "toluene" as the reaction solvent which does not fall within those solvents presently claimed, and, finally, the product formed in Example 8 is an "n-decyl-3-isothiazolon" which is not among the compounds claimed in Formula III.

Since neither Kim et al. nor Lewis et al. alone explicitly or implicitly teach all the claimed features and do not suggest modifying the teachings therein to employ chlorine (Cl_2) in conjunction with a reaction solvent which has little or no solubility for hydrogen chloride and such that the ratio of chlorine to either A-1 or A-2 of Kim et al. or Formulae III or IV Lewis et al. will yield a 2-alkyl-4-isothiazoline-3-one containing virtually no mutagenic 5-chloro-2-alkyl-4-isthiazoline-3-one, the Examiner has not set forth a *prima case* of obviousness over Lewis et al. alone or in combination with Kim et al. Additionally, since Kim et al. teach (page 11, lines 13-18) that mixtures of a major proportion of 3-isothiazolin-3-one relative to the 5-chloro-3-isothiazolin-3-one will yield a "biologically ineffective" mixture while preferring biologically active mixtures which contain a majority of the 5-chloro-3-isothiazolin-3-one relative to the 3-

isothiazolin-3-one, one of ordinary skill in the prior art upon combining the teachings of Lewis et al and Kim et al. would be lead away from modifying the process of Lewis et al. (or Kim et al.) to optimize the production of 3-isothiazolin-3-one relative to the 5-chloro-3-isothiazolin-3-one.

In summary, the presently claimed inventive process requires the use of chlorine (Cl_2) as the chlorinating agent in conjunction with a solvent, in which hydrogen chloride is insoluble or has low solubility, in a ratio of chlorine to Formula I of 3:1 or in a ratio of chlorine to Formula II of 2:1 wherein the 2-alkyl-4-isothiazoline-3-one of Formula III produced is essentially free of 5-chloro-2-alkyl-4-isothiazoline-3-one or contains less than 1.0% of 5-chloro-2-alkyl-4-isothiazoline-3-one. Since neither reference teaches each and every feature of the claimed invention, nor suggests the use of chlorine (Cl_2) with the particularly claimed solvent to achieve the purity yields claimed for 2-alkyl-4-isothiazoline-3-one of Formula III, a *prima facie* case of obviousness has not been established for either Lewis et al. or Kim et al. alone, or the combination of references. (see MPEP Chapters 2142 and 2143). In addition, there is no likelihood of success of achieving the claimed invention upon combining the teachings of Kim et al. with Lewis et al. since:

> 1) Kim et al. explicitly require that the processing be carried out to <u>have significant amounts</u> of 5-chloro-2-alkyl-4-isothiazoline-3-one in the final product; while Lewis et al. set forth that each process of forming an isothiazoline-3-one within the scope of the claimed invention (Examples 2, 5, 14) will necessarily have a substantial amount of halogenated component as well, and since,
>
> 2) Kim et al. explicitly state that mixtures in which 3-isothiazolin-3-one is a major proportion relative to the 5-chloro-3-isothiazolin-3-one will yield a "biologically ineffective" mixtures.

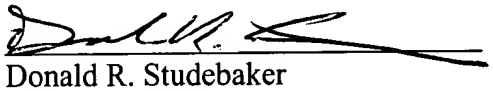
These interests are completely incompatible and provide no suggestion/motivation or likelihood of success in achieving the claimed invention even if combined.

Therefore, the rejection of claims 1-23, under 35 U.S.C. 103(a), as being unpatentable over GB 2,308,364 to Kim et al. or U.S. Patent No. 3,849,430 to Lewis et al., each taken alone or in combination with each other has been set forth in error and should be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present application should now be in condition for allowance. The Examiner's reconsideration and withdrawal of the present rejections is respectfully requested. An early Notice of Allowance is courteously

solicited. However, should the Examiner believe that there are further issues remaining to be resolved to place the application in condition for allowance, she is invited to contact the undersigned.

Respectfully submitted,



Donald R. Studebaker
Reg. No. 32,815

NIXON PEABODY LLP
8180 Greensboro Drive, Suite 800
McLean, Virginia 22102
(703) 770-9300

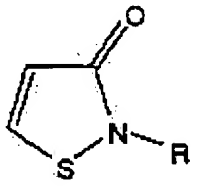
VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

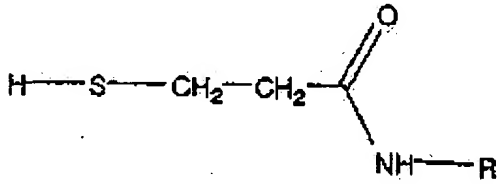
Please amend claims 13 and 20 to read as follows:

13. (Amended) A method of producing 2-alkyl-4-isothiazoline-3-one stated in claim 1 in which aforementioned solvent is inert to the compounds of formula (I), formula (II), formula (III), and to the chlorinating agent, and in which the solubility of hydrogen chloride at normal temperature/pressure is less than 0.04 in molar fraction.

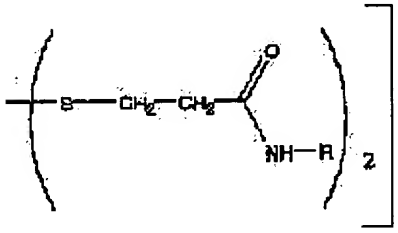
20. (Amended) A method of producing 2-alkyl-4-isothiazoline-3-one represented by the general formula (III),



wherein the compound represented by formula (I),



[or alternatively, the compound represented by formula (II),



is reacted with chlorine (Cl_2) as a chlorinating agent in a solvent,

wherein the molar-equivalent ratio of said chlorinating agent to the compound of formula (I) is 2:1[, or alternatively,

wherein the molar-equivalent ratio of said chlorinating agent to said the compound of formula (II) is 3:1],

wherein R in the compounds of formulas (I)[, (II),] and (III) represents C1 to C8 alkyl groups or aralkyl groups, and

wherein the 2-alkyl-4-isothiazoline-3-one of Formula III produced contains less than 1.0% of 5-chloro-2-alkyl-4-isothiazoline-3-one.